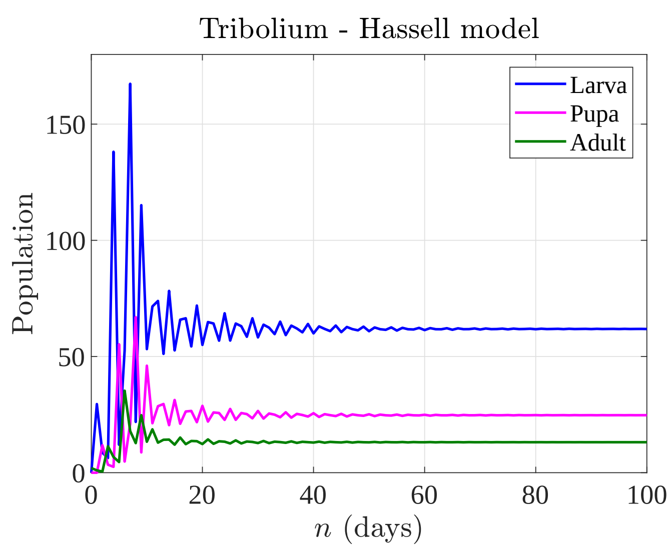
1. a. An age-structured model for *Tribolium* is given by:

$$\begin{aligned} L_{n+1} &= \frac{bA_n}{(1+c_{ea}A_n+c_{el}L_n)^4}, \\ P_{n+1} &= s_l L_n, \\ A_{n+1} &= \frac{P_n}{(1+c_{pa}A_n)^4}+s_a A_n, \end{aligned}$$

with parameters, $b = 15$, $s_l = 0.4$, $s_a = 0.5$, $c_{ea} = 0.002$, $c_{el} = 0.005$, and $c_{pa} = 0.03$. A simulation of this system starting with $(L_0, P_0, A_0) = (0, 0, 2)$ yielded the table of populations:

n	L	P	A
0	0	0	2
10	53.190	46.049	13.314
20	54.998	28.770	12.329
30	58.216	26.580	12.760
50	60.880	25.144	13.058
100	61.833	24.750	13.121

A graph of this simulation is shown below:



b. It is easy to see that one equilibrium is the extinction equilibrium with $(L_e, P_e, A_e) = (0, 0, 0)$. Numerically, we can solve to find the positive equilibrium and find $(L_e, P_e, A_e) = (61.8594, 24.7437, 13.1201)$. The Jacobian matrix for this system is readily computed and gives:

$$J(L,P,A) = \begin{pmatrix} \frac{-0.3\,A}{(1+0.002\,A+0.005\,L)^5} & 0 & \frac{15\,(1-0.006\,A+0.005\,L)}{(1+0.002\,A+0.005\,L)^5} \\ 0.4 & 0 & 0 \\ 0 & \frac{1}{(1+0.03\,A)^4} & \frac{-0.12\,P}{(1+0.03\,A)^5}+0.5 \end{pmatrix}.$$

About the extinction equilibrium, the Jacobian matrix becomes:

$$J(0,0,0) = \begin{pmatrix} 0 & 0 & 15 \\ 0.4 & 0 & 0 \\ 0 & 1 & 0.5 \end{pmatrix},$$

which has eigenvalues $\lambda_1 = 2$ and $\lambda_{2,3} = -0.75 \pm 1.56125\,i$. All of these eigenvalues satisfy $|\lambda| > 1$, so this equilibrium is clearly unstable.

About the positive equilibrium, the Jacobian matrix becomes:

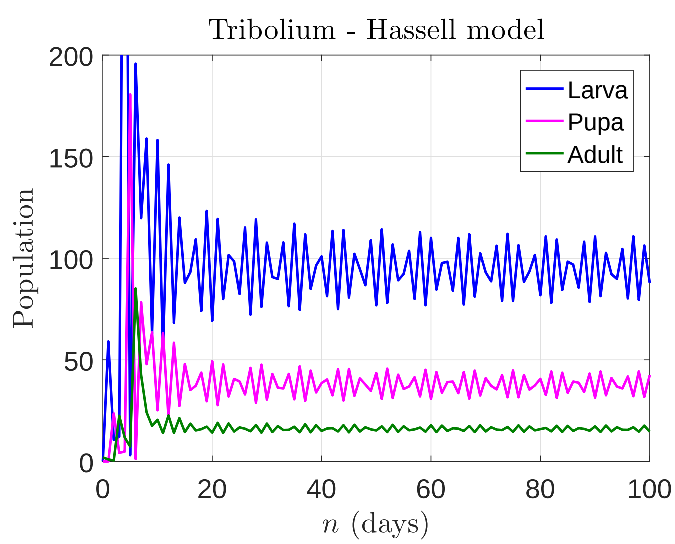
$$J(61.8594, 24.7437, 13.1201) = \begin{pmatrix} -0.92636 & 0 & 4.34430 \\ 0.4 & 0 & 0 \\ 0 & 0.26512 & -0.06487 \end{pmatrix},$$

which has eigenvalues $\lambda_1 = 0.53079$ and $\lambda_{2,3} = -0.76101 \pm 0.53743\,i$. Note the $|\lambda_{2,3}| = 0.93165$, so all of these eigenvalues satisfy $|\lambda| < 1$, so this equilibrium is clearly stable, which is readily seen in the simulation. Since this equilibrium is stable, it attracts all positive solutions. The result is a stable population distribution that consists of 62.031% larva, 24.812% pupa, and 13.157% adult *Tribolium* beetles.

c. With $b = 30$ the age-structured model above is again simulated starting with $(L_0, P_0, A_0) = (0, 0, 2)$ and yielded the table of populations:

n	L	P	A
0	0	0	2
10	158.191	25.171	20.504
20	69.227	49.329	14.204
30	107.690	30.434	18.653
50	76.843	43.543	15.249
100	87.855	42.503	14.632

A graph of this simulation (not showing the peak of larva $L_4 = 451.54$) is shown below:



Once again one equilibrium is the extinction equilibrium with $(L_e, P_e, A_e) = (0, 0, 0)$. Numerically, we can solve to find the positive equilibrium and find $(L_e, P_e, A_e) = (93.7504, 37.5001, 15.8385)$. The Jacobian matrix for this system is readily computed and gives:

$$J(L,P,A) = \begin{pmatrix} \frac{-0.6\,A}{(1+0.002\,A+0.005\,L)^5} & 0 & \frac{30\,(1-0.006\,A+0.005\,L)}{(1+0.002\,A+0.005\,L)^5} \\ 0.4 & 0 & 0 \\ 0 & \frac{1}{(1+0.03\,A)^4} & \frac{-0.12\,P}{(1+0.03\,A)^5} + 0.5 \end{pmatrix}.$$

About the extinction equilibrium, the Jacobian matrix becomes:

$$J(0,0,0) = \begin{pmatrix} 0 & 0 & 30 \\ 0.4 & 0 & 0 \\ 0 & 1 & 0.5 \end{pmatrix},$$

which has eigenvalues $\lambda_1 = 2.4688$ and $\lambda_{2,3} = -0.9844 \pm 1.9727\,i$. All of these eigenvalues satisfy $|\lambda| > 1$, so this equilibrium is clearly unstable.

About the positive equilibrium, the Jacobian matrix becomes:

$$J(93.7504, 37.5001, 15.8385) = \begin{pmatrix} -1.24965 & 0 & 5.41930 \\ 0.4 & 0 & 0 \\ 0 & 0.21118 & -0.14421 \end{pmatrix},$$

which has eigenvalues $\lambda_1 = 0.45161$ and $\lambda_{2,3} = -0.92273 \pm 0.40275\,i$. Note the $|\lambda_{2,3}| = 1.0068$. It follows that the complex eigenvalues satisfy $|\lambda_{2,3}| > 1$, so this equilibrium is unstable, which is readily seen in the simulation. This equilibrium is barely unstable, so the oscillations have fairly low amplitude. From the positive equilibrium, the age-structured population distribution remains near 63.737% larva, 25.495% pupa, and 10.768% adult *Tribolium* beetles.

d. The eigenvalues $\lambda_{2,3}$ are very close in magnitude to one, which is where the Hopf bifurcation occurs. One creates a program to find the equilibrium as b varies, then the Jacobian matrix is computed and its eigenvalues are found. A bisection method is used to determine the value of b when $|\lambda_{2,3}| = 1$, and this occurs when $b = 28.1801$ (between $b = 28.18007$ and $b = 28.18008$).

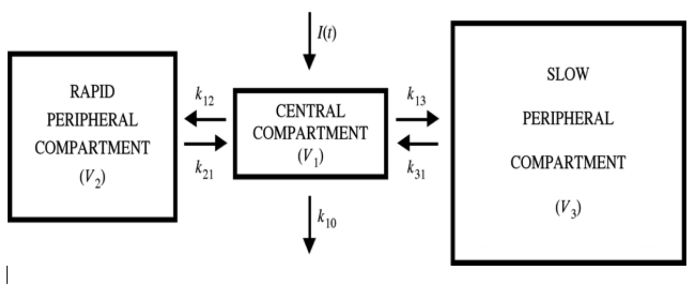
2. a. A pair of dice have 36 possible outcomes, which for fair dice occur equally likely. Since there are six ways to obtain a 7, this means that fair dice have a $\frac{1}{6} = 0.166667$ chance of obtaining a 7. From the assumptions on the loaded dice, we can easily compute that obtaining a 2, 3, 4, or 5 is $p = \frac{1}{6.5} = 0.153846$. The 6 on the first die and 1 on the second die each has a probability 0.307692, while the 1 on the first die and 6 on the second die each has a probability 0.0769231. The six possible means of obtaining a 7 have the following probability:

$$P(7) = 4\left(\frac{1}{6.5}\right)^2 + \left(\frac{2}{6.5}\right)^2 + \left(\frac{0.5}{6.5}\right)^2 = 0.195266.$$

It is just as likely that you obtain the loaded 7 ($P = 0.0946746$) as obtained with 2 and 5 or 3 and 4. The MatLab dice program given in class was modified to reflect the different probabilities of the loaded dice. When a simulation of throwing these dice 10,000 times was performed 3 times, it was easy to show that a 7 occurred 1971, 1978, and 1907 times, which is consistent with the theoretical expected value.

b. The dice were rolled twice and added 10,000 times, then to show consistency, the process was repeated three times. The three separate means were 14.0043, 14.0104, and 13.9914 with respective standard deviations of 3.3635, 3.3653, and 3.3841. This process was repeated with fair dice, the three separate means were 14.0321, 13.9711, and 13.9667 with respective standard deviations of 3.4224, 3.3770, and 3.4300. The means are clearly the same for both fair and loaded dice, but the standard deviation increased slightly for the fair dice.

3. a. The three compartment model for fentanyl seen in the figure below is given by the system of differential equations that follows.



The system of differential equations satisfies:

$$\begin{aligned}
\dot{C}_1 &= -(k_{10}+k_{12}+k_{13})C_1 + k_{21}C_2 + k_{31}C_3, \qquad C_1(0) = I_0,\\
\dot{C}_2 &= k_{12}C_1 - k_{21}C_2, \qquad C_2(0) = 0,\\
\dot{C}_3 &= k_{13}C_1 - k_{31}C_3, \qquad C_3(0) = 0.
\end{aligned}$$

b. Since the experiment only measures blood concentration, we should only be examining $C_1(t)$. It is expected that this solution should only contain decaying exponentials, so has the form:

$$C_1(t) = a_1e^{-\lambda_1 t} + a_2e^{-\lambda_2 t} + a_3e^{-\lambda_3 t}. \tag{1}$$

The DE above can be written in matrix form as follows:

$$\dot{C}_1 = \begin{pmatrix} -(k_{10}+k_{12}+k_{13}) & k_{21} & k_{31} \\ k_{12} & -k_{21} & 0 \\ k_{13} & 0 & -k_{31} \end{pmatrix} C_1.$$

The challenge is showing that all the eigenvalues of this matrix are real and negative. Physically, the two peripheral compartments are closed to the outside and the central/plasma compartment loses fentanyl through filtration and metabolism. It follows that there must only be an exponential decay of fentanyl in the blood compartment, which drives the other compartments, so all three compartments in this model must exhibit exponential decay. However, the general characteristic equation of the matrix above is given by:

$$\lambda^3 + (k_{10}+k_{12}+k_{13}+k_{21}+k_{31})\lambda^2 + ((k_{10}+k_{13}+k_{31})k_{21} + k_{31}(k_{10}+k_{12}))\lambda + k_{10}k_{21}k_{31} = 0,$$

and its three roots are very complicated, making it hard to prove they are all real.

The cubic polynomial is of the form: $\lambda^3 + a_2\lambda^2 + a_3\lambda + a_0 = 0$. The Routh-Hurwitz Criterion for cubic polynomials, showing that all eigenvalues have negative real part, reduces to $a_2 > 0$, $a_0 > 0$, and $a_2 a_1 > a_0$. These conditions are clearly satisfied showing stability of the DE. However, it only proves that one eigenvalue is negative. If you add the condition that $k_{12} = k_{21}$ and $k_{13} = k_{31}$, then the matrix becomes symmetric, so all eigenvalues are real. This combined with the Routh-Hurwitz Criterion would prove that all three eigenvalues are negative. If $k_{12} = k_{21} = k_{13} = k_{31} = k$, then Maple readily solves the characteristic equation and gives strictly negative eigenvalues. The general case, showing 3 negative eigenvalues, is not demonstrated here. The three negative eigenvalues can be ordered, $-\lambda_1 < -\lambda_2 < -\lambda_3$, where λ_1 represents the *rapid distribution phase*, λ_2 represents the *middle distribution phase*, and λ_3 represents the *terminal/elimnation phase*, as $-\lambda_1$ results in the most rapid decay, while $-\lambda_3$ gives the slowest decay.

c. Details for the solution to this problem can be found in the lecture notes at https://jmahaffy.sdsu.edu/courses/f16/math541/beamer/lst_sq-04.pdf. Specifically the details are on Slides 73-80. The model found by exponential peeling is given by:

$$C_1(t) = 8.1514\, e^{-0.1601t} + 1.6396\, e^{-0.02078t} + 0.6083\, e^{-0.003794t}.$$

The sum of square errors is $J_1(a_1, a_2, a_3) = 3.4859$. The sum of square errors found by comparing the logarithm of the data to the logarithm of the model gives $J_2(a_1, a_2, a_3) = 0.12778$.

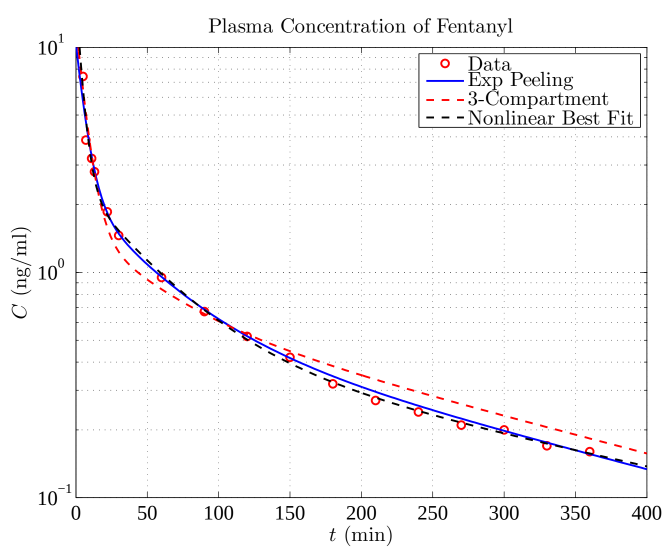
d. With the 6 parameters from the exponential peeling (3 coefficients and 3 exponents) we apply MatLab's `fminsearch` (Nonlinear Least Squares fit) to find the best fitting parameters for the 3-compartment model. We perform a least squares best fit of the logarithm of the model to the logarithm of the data, starting with the initial guess from the exponential peeling model and minimizing:

$$J_3(p) = \min_p \left(\ln(C_i) - \ln(p_1 e^{-p_2 t} + p_3 e^{-p_4 t} + p_5 e^{-p_6 t})\right)^2.$$

The result is

$$C_1(t) = 14.1472 e^{-0.24226t} + 2.0063 e^{-0.020695t} + 0.4928 e^{-0.0031957t},$$

which has the sum of square errors $J_3(p) = 0.08607$ and improves on the exponential peeling fit. Below is a graph of these models (along with another model not discussed here).



We see that the differences between the exponential peeling model and the nonlinear fit models are quite small both visually and from their sum of square errors. The nonlinear fit is a very sensitive problem and requires a very good initial guess, which is a problem for this approach. However, the graph shows that it is an excellent fit to the experimental data. The exponential peeling procedure is fairly easy by just requiring linear fits to the logarithms of the data, and this model does a very good job fitting the data also. The exponential peeling method does suffer from having an element of non-objectivity where the user makes an arbitrary decision on the boundaries of the different phases of the model. In addition, it can be hard deciding on the number of compartments that should be used.

4. a. We consider the system of delay differential equations given by:

$$\begin{aligned}
\frac{dx_1(t)}{dt} &= \frac{a_1}{1+k_1x_3^2(t-r)} - b_1x_1(t),\\
\frac{dx_2(t)}{dt} &= \frac{a_2x_1^2(t)}{1+k_2x_1^2(t)} - b_2x_2(t),\\
\frac{dx_3(t)}{dt} &= a_3x_2(t) - b_3x_3(t),
\end{aligned}$$

where a_i are production rates, b_i are decay constants, k_i are kinetic constants, and r is the delay for the various processes. The equilibrium is found solving the right hand side of the above equation equal to zero. Using a nonlinear solver, we solve

$$\frac{a_1}{1+k_1x_{3e}^2} - b_1x_{1e} = 0, \qquad \frac{a_2x_{1e}^2}{1+k_2x_{1e}^2} - b_2x_{2e} = 0, \qquad a_3x_{2e} - b_3x_{3e} = 0,$$

with the parameters $a_i = 1$, $b_i = 0.5$, and $k_i = 1$. There is a unique equilibrium due to the increasing nature of the positive terms of the last two equations and the decreasing form of the first term in the first equation. The resulting equilibrium is:

$$(x_{1e}, x_{2e}, x_{3e}) = (0.71184, 0.67261, 1.34522).$$

The Jacobian matrix for the nonlinear ODE satisfies:

$$J(x_1,x_2,x_3) = \begin{pmatrix} -b_1 & 0 & \frac{-2\,a_1k_1x_3}{\left(1+k_1x_3^2\right)^2} \\ \frac{2\,a_2x_1}{\left(1+k_2x_1^2\right)^2} & -b_2 & 0 \\ 0 & a_3 & -b_3 \end{pmatrix}.$$

With the particular parameters and the equilibrium, we can linearize the ODE by letting $y_1(t) = x_1(t) - x_{1e}$, $y_2(t) = x_2(t) - x_{2e}$, and $y_3(t) = x_3(t) - x_{3e}$, giving the linearized system:

$$\begin{pmatrix} \dot{y}_1 \\ \dot{y}_2 \\ \dot{y}_3 \end{pmatrix} = \begin{pmatrix} -0.5 & 0 & -0.340823 \\ 0.627118 & -0.5 & 0 \\ 0 & 1 & -0.5 \end{pmatrix} \begin{pmatrix} y_1 \\ y_2 \\ y_3 \end{pmatrix}.$$

This has the characteristic equation given by:

$$\lambda^3 + 1.5\,\lambda^2 + 0.75\,\lambda + 0.338736 = 0,$$

which produces the eigenvalues

$$\lambda_1 = -1.097897 \quad \text{and} \quad \lambda_{2,3} = -0.201052 \pm 0.517794\, i.$$

All of the eigenvalues have negative real part, so it follows that the system of differential equations has its equilibrium being asymptotically stable.

b. The linearization of the system of delay differential equations about the equilibrium follows in a manner similar to the class notes, and with the same change of variables given above we obtain the following:

$$\begin{aligned} \begin{pmatrix} \dot{y}_1(t) \\ \dot{y}_2(t) \\ \dot{y}_3(t) \end{pmatrix} &= \begin{pmatrix} -0.5 & 0 & 0 \\ 0.627118 & -0.5 & 0 \\ 0 & 1 & -0.5 \end{pmatrix} \begin{pmatrix} y_1(t) \\ y_2(t) \\ y_3(t) \end{pmatrix} + \begin{pmatrix} 0 & 0 & -0.340823 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} \begin{pmatrix} y_1(t-r) \\ y_2(t-r) \\ y_3(t-r) \end{pmatrix} \\ \dot{\mathbf{y}}(t) &= A\mathbf{y}(t) + B\mathbf{y}(t-r). \end{aligned}$$

As usual, we attempt a solution of the form $\mathbf{y}(t) = \xi\, e^{\lambda t}$, which following class notes gives:

$$\begin{aligned} \lambda \xi I e^{\lambda t} &= A\xi\, e^{\lambda t} + B\xi\, e^{\lambda(t-r)} \\ (A + B\, e^{-\lambda r} - \lambda I)\xi &= \mathbf{0}. \end{aligned}$$

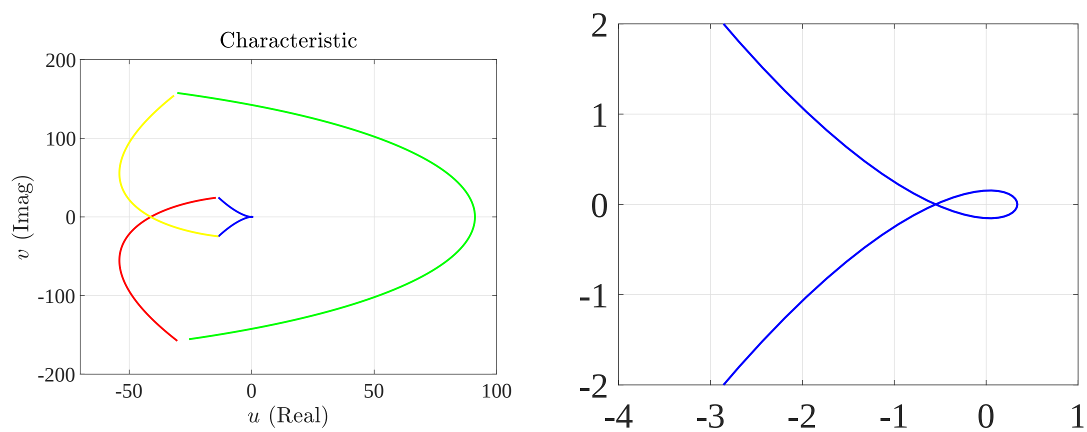
This leads to the characteristic equation:

$$\det |A + B\, e^{-\lambda r} - \lambda I| = 0,$$

which is equivalent to the characteristic equation:

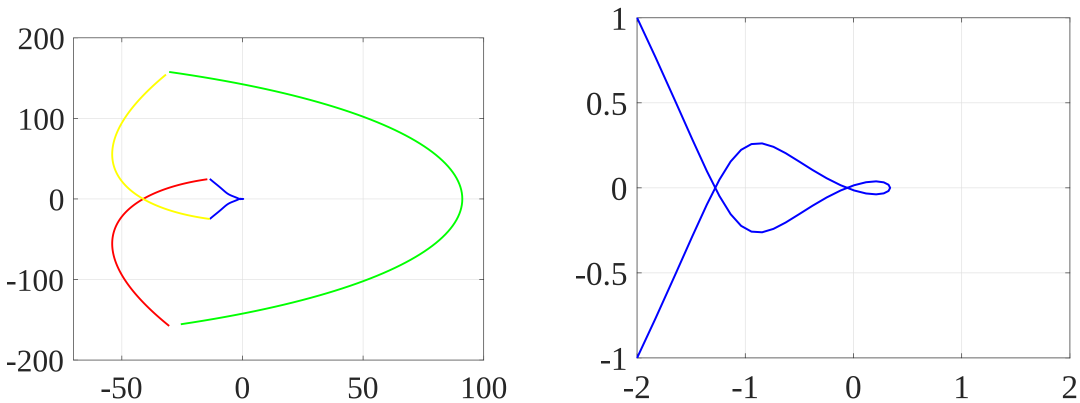
$$\lambda^3 + 1.5\,\lambda^2 + 0.75\,\lambda + 0.125 = -0.213736\, e^{-\lambda r}.$$

This characteristic equation maps the contour of the perimeter of rectangle in the complex plane bounded by $0 \le x \le 4$ and $-3 \le y \le 3$ in the counterclockwise direction into the complex image space. The figure below shows the image when $r = 1$. The figure on the left shows the entire image plot, while the figure on the right shows the image blown up near the origin.

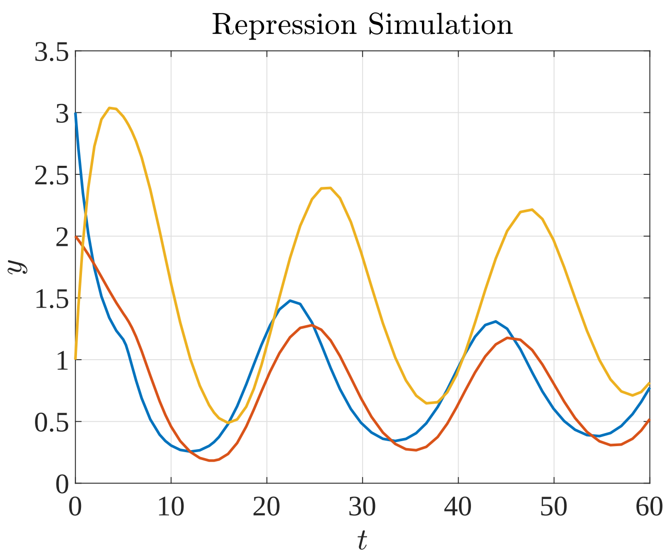


Following this image plot, we see a clockwise and a counter-clockwise encirclement of the origin. Thus, the net counter-clockwise encirclements of the origin are zero, so there are no zeroes of the characteristic equation, which suggests that this model with a delay of $r = 1$ is asymptotically stable. (Simulation of this model with this delay does show stability of the model.)

Next the same program is applied with $r = 5$ in the figure below. The figure on the left shows the entire image plot, while the figure on the right shows the image blown up near the origin.



Following this image plot, we see two counter-clockwise encirclements of the origin. Thus, there are two zeroes of the characteristic equation inside the rectangle noted above, which shows there are at least two eigenvalues with positive real parts. Thus, this model with a delay of $r = 5$ is unstable. (Simulation of this model with this delay shows sustained oscillations, so the equilibrium of the model is unstable, as seen below.)



This rectangular region shows that the frequency is bounded by 3, so the period must be greater than $\frac{2\pi}{3} \approx 2$. The actual period from the simulation is approximately 20.

c. Inserting $\lambda = i\omega$ into the characteristic equation gives:

$$-\omega^3 i - 1.5\,\omega^2 + 0.75\,\omega i + 0.125 = -0.213736(\cos(\omega r) - i\sin(\omega r)).$$

Breaking this equation into the real and imaginary parts gives the two equations:

$$\begin{aligned} -1.5\,\omega^2 + 0.125 &= -0.213736\,\cos(\omega r), \\ -\omega^3 + 0.75\,\omega &= 0.213736\,\sin(\omega r). \end{aligned}$$

These equations are inserted into Maple's *fsolve*, and one solution is

$$r = 4.271916 \qquad \text{and} \qquad \omega = 0.327842.$$

This is the smallest value of r, giving where the Hopf bifurcation occurs. It follows that the repression model loses stability at $r = 4.271916$, and from the frequency $\omega = 0.327842$ we obtain the period $\frac{2\pi}{\omega} = 19.165294$.